REMARKS

Status Summary

Claims 47, 51-65, and 68 are pending and subject to the advisory action mailed 8 February 2007. Claims 1-46, 48-50, and 66-67 were canceled previously. Claim 64 is rejected under 35 U.S.C. §112, first paragraph, as allegedly presenting new matter. Claims 47, 51-63, 65 and 68 remain rejected under 35 U.S.C. § 103(a) as allegedly obvious over US Patent No. 5,695,770 to Raychaudhuri in view of Woodworth et al. (1996) *Cell Growth & Differentiation* 7:811-820, PCT International Publication No. WO 94/09815 to Segarini et al., as evidenced by Schmolka et al. (1977) *J. Am. Oil Chem. Soc.* 54:110-116, Schultz-Cherry et al. (1995) *J. Biol. Chem.* 270(13):7304-10, and/or PCT International Publication No. WO 91/08298 to Capon et al. Claims 47, 51-65, and 68 are rejected under the judicially created obviousness type double patenting over US Patent No. 6,998,125.

In the present response, claim 64 is amended. Reconsideration is respectfully requested in view of the foregoing amendment and following remarks.

35 U.S.C. §112, First Paragraph, Written Description - New Matter

Claim 64 is rejected under 35 U.S.C. §112, first paragraph, because the specification allegedly does not describe the claimed method "wherein the antigen formulation contains no more than 20 micrograms of an immunostimulating muramyl dipeptide" in such a way as to convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time the application was filed, in compliance with the requirement for written description of 35 U.S.C. §112, first paragraph. The examiner alleges that the specification "only teaches not to use muramyl dipeptide" and that "there is nothing in the specification to teach or suggest **use** of an antigen formulation containing no more than 20 micrograms of an immunostimulating muramyl dipeptide in the claimed method…." In support of this allegation, the examiner points to two sentences on lines 9-11 of page 12, which teach that it is important that a muramyl dipeptide (MDP) be lacking from the adjuvant formulation of the invention, because "such a peptide will interfere with induction of a CTL response if it [is] provided in an

amount greater than about 20 micrograms per normal human formulation administration." Advisory Action, pages 3-4.

Applicants have previously submitted that the specification **does** describe the method of claim 64 in a manner such that one of skill in the art at the time the application was filed would recognize that that the inventors had possession of the claimed invention "wherein the antigen formulation contains no more than 20 micrograms of an immunostimulating muramyl dipeptide." In particular, the text of the specification cited by the examiner describes the invention wherein peptides such as MDP are completely absent as a "preferred embodiment," it describes that peptides such as MDP can provide the advantage of enhancing the humoral response, and it expressly describes that more than 20 micrograms of a peptide such as MDP interferes with induction of a CTL response. When the context of the cited text is considered, one of skill in the art would clearly understand from the description on page 12 that the importance that an MDP be "lacking" from the adjuvant formulation of the invention does not simply describe complete absence of MDP from the adjuvant formulation, but also describes the method of the invention in which MDP is present in an amount sufficiently low (*i.e.*, $\leq$ 20 micrograms per normal human formulation administration) that the MDP does not interfere with induction of a CTL response.

Upon consideration of the foregoing arguments, the examiner acknowledges that a method wherein the antigen formulation contains no more than 20 micrograms of an immunostimulating MDP can be practiced. However, the examiner maintains that the specification does not teach or suggest such a method. Advisory action, pages 3-4.

In further response to the rejection of claim 64 and consistent with applicants' prior arguments, applicants additionally submit that the specification describes at page 10, lines 13-15, that the CTL-inducing composition of the invention includes an "antigen formulation [that] preferably lacks any immunostimulating peptide component, or has sufficiently low levels of such a component that the desired cellular response is not diminished" (emphasis added). As described throughout the specification, muramyl dipeptide (MDP) is a representative immunostimulatory peptide. To clarify that this aspect of the invention is fully supported by the original disclosure, claim 64 is amended to specify that the antigen formulation contains "sufficiently low levels of an immunostimulating peptide that a cellular response is not diminished," as described at page 10. Applicants further assert that one skilled in the art would be able to readily assess a sufficiently low level of an immunostimulating peptide based upon the

measurable outcome of a cellular immune response. The originally filed specification provides such guidance, noting that an amount of 20 micrograms of MDP per normal human formulation administration is not a sufficiently low level given that it interferes with the CTL response.

Based upon the foregoing, the method as set forth in claim 64 does not constitute new matter, and withdrawal of the rejection of claim 64 under 35 U.S.C. §112, first paragraph, for alleged lack of written description is respectfully requested.

Rejection of Claims Under 35 U.S.C. §103(a)

Based Upon Raychaudhuri, Woodworth, Segarini, and Schmolka

Claims 47, 51-63, and 65-68 remain rejected under 35 U.S.C. § 103(a) as allegedly obvious over U.S. Patent No. 5,695,770 to Raychaudhuri et al. ("Raychaudhuri") in view of Woodworth et al. (1996) *Cell Growth & Differentiation* 7:811-820 ("Woodworth"), PCT International Publication No. WO 94/09815 to Segarini et al. ("Segarini"), as evidenced by Schmolka et al. (1977) *J. Am. Oil Chem. Soc.* 54:110-116 ("Schmolka"). Advisory Action, pages 4-7.

It is the examiner's burden to establish a *prima facie* case of obviousness, which requires: (1) some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine the reference teachings; (2) the teaching or suggestion of all the claim limitations of the applicant's invention in the combined prior art references; and (3) a reasonable expectation of success. MPEP § 2143. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). The mere fact that the references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990) MPEP § 2143.01 III. Greater than expected results are evidence of non-obviousness, and in making a determination of patentability, such evidence in support of patentability must be weighed against evidence supporting a *prima facie* case. MPEP §§ 716.01(d) and 716.02.

In response to the rejection of claims under section 103(a), applicants respond that the examiner has failed to meet the burden of a *prima facie* case because one of skill in the art would not have a reasonable expectation of success in performing the claimed combination method. In addition, the combined teachings of the references do not teach or suggest the unexpected synergistic effects of the claimed combination, *i.e.*, that an agent capable of neutralizing, blocking, antagonizing, or down regulating the activity or preventing activation of transforming growth factor-β (TGFβ) can be used to enhance an antigen-specific cytoxic T cell lymphocyte response that is otherwise ineffective.

The teachings of Raychaudhuri, Woodworth, Segarini, and Schmolka have been summarized previously. As acknowledged by the examiner, Raychaudhuri does not teach a method for enhancing an antigen-specific CTL response that includes administration of an agent capable of neutralizing, blocking, antagonizing, or down regulating the activity or preventing activation of transforming growth factor-β (TGFβ). Official Action mailed 8 September 2006, page 28. The examiner relies on Woodworth as teaching that TGFβ1 stimulates the growth of HPV-immortalized keratinocytes. The examiner relies on Segarini as teaching that TGFβ can cause immunosuppression and suggests administering an anti-TGFβ antibody to counteract the immunosuppression (*see* page 2, second paragraph), and further as teaching administering a TGFβ-binding receptor fragment to increase the effectiveness of a vaccine (*see* page 6). The examiner relies on Schmolka as teaching the chemical structure of poloxamer 401. Thus, the examiner alleges that, at the time the invention was made, it would have been obvious for one of ordinary skill in the art to modify the method of Raychaudhuri by co-administering a TGFβ-antagonizing agent such as an anti-TGFβ antibody or a TGFβ-binding receptor fragment, since inhibition of TGFβ activity would allegedly have been expected to increase vaccine efficacy as described by Segarini, or to prevent TGFβ from stimulating growth of HPV-infected cells as described by Woodworth.

In response to the outstanding rejection, applicants have previously submitted arguments and supporting abstracts that demonstrate conflicting reports of the ability of TGFβ to inhibit growth of HPV-positive cells. Upon consideration of such arguments, the examiner is unpersuaded because the supporting abstracts allegedly do not provide or support evidence that TGFβ inhibits growth of HPV-immortalized cells under conditions that induce squamous

differentiation. Further, the examiner contends that Woodworth clearly teaches that conditions that induce squamous differentiation are necessary for growth induction by TGFβ. Advisory action, pages 5-7.

In response to the examiner's comments in the advisory action, applicants submit the complete text of Ozbun et al. (1996) *J. Virol.* 70(8):5437-5446. As one example of reports of TGFβ activity that are contrary to that of Woodworth, this reference shows that TGFβ induces HPV-positive keratinocytes and cervical cancer cells to differentiate in a tissue culture system that models conditions *in vivo*. Specifically, Ozbun describes that the authors have "employed an organotypic tissue culture system which emulates the three-dimensional architecture and differentiation scheme of keratinocytes in vivo" (page 5438, column 1). Thus, contrary to the assertion of the examiner, the results of Ozbun were obtained under conditions that support differentiation. As asserted previously, these results are *directly opposite* to those of Woodworth. In view of such conflicting results, *i.e.*, that TGFβ can either promote or inhibit proliferation of HPV-positive keratinocytes, and specifically that TGFβ inhibits proliferation of cervical cancer cells, one of skill in the art would not readily conclude that the presently claimed combination method could be performed with a reasonable chance of success.

Moreover, when considering the combined teachings of Raychaudhuri, Ozbun, and Segarini, one skilled in the art would have considered that this combination of references, available at the time of the instant invention, actually *teaches away* from the claimed methods. A prior art reference may be considered to teach away when "a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by applicant" *In re Gurley*, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994). Based upon Ozbun, one skilled in the art would have been discouraged from using an inhibitor of TGFβ activation to thereby elicit an anti-tumor response, given that Ozbun teaches a role for TGFβ in induction of cervical cancer cell differentiation.

Applicants further respond that a skilled artisan could not have reasonably predicted that the combined use of an antigen formulation and an agent that inhibits TGFβ activation would elicit synergistic CTL-inducing responses as described in the instant application. The term "synergistic" is understood in the art to mean a greater than additive effect. *See e.g.*, Merriam-

Webster Dictionary (1997), which defines synergistic as "interaction of discrete agencies (as industrial firms), agents (as drugs), or conditions such that the total effect is greater than the sum of the individual effects" (copy enclosed). When combining different therapeutic regimens, for example, CTL-inducing formulations and agents for inhibition of TGFβ immunosuppression, which have distinct biological effects based upon modulation of different cellular functions, there is no basis for predicting a greater than additive therapeutic effect. Rather, a skilled artisan would at best predict an additive effect.

A synergistic effect of a CTL-inducing antigen formulation in combination with an inhibitor of TGFβ activation, as presently claimed, could only be known once experimental evidence demonstrating such responses was available, as first disclosed in the instant application. In particular, Figures 2A-2B demonstrate the anti-tumor activity of E7-PROVAX® when used in combination with an inhibitory anti-TGFβ antibody. Figure 2A shows that administration of E7-PROVAX® had no effect on tumor growth, *i.e.*, the response closely tracked that of tumor-bearing animals that received no treatment (control). Likewise, administration of an inhibitory anti-TGFβ antibody showed a minimal anti-tumor response that also closely tracked the control. By contrast, animals receiving both agents showed marked inhibition of tumor growth. Thus, a previously inactive single agent, E7-PROVAX®, was rendered effective by use in combination with a second agent, an anti-TGFβ antibody. The outcome of the combined treatment is synergistic or greater than additive, *i.e.*, more than the sum of zero effect (the effect of E7-PROVAX® as a single agent) plus the effect of the inhibitory anti-TGFβ antibody. Figure 2B shows similar results. The effect of repeated administration of an anti-TGFβ antibody increases its anti-tumor response, however, the combined effect of E7-PROVAX® plus anti-TGFβ antibody is still synergistic or greater than additive. As required to support a showing of non-obviousness, the evidence relied on by the applicant upon establishes "that the differences in results are in fact unexpected and unobvious and of both statistical and practical significance." *Ex parte Gelles*, 22 USPQ2d 1318, 1319 (Bd. Pat. App. & Inter. 1992) MPEP § 716.02(b) I.

Based upon the foregoing, the cited references do not establish a *prima facie* case of obviousness, and the applicants respectfully request that the rejection of claims 47, 51-63, and

65-68 under 35 U.S.C. §103(a) as allegedly being unpatentable over Raychaudhuri in view of Woodworth and Segarini, and as evidenced by Schmolka, be withdrawn.

Rejection of Claims Under 35 U.S.C. §103(a)

Based Upon Raychaudhuri, Woodworth, Segarini, Schmolka, Schultz-Cherry, and Capon

Claim 47 is rejected under 35 U.S.C. §103(a) as allegedly obvious over Raychaudhuri in view of Woodworth and Segarini, as evidenced by Schmolka, and further in view of Schultz-Cherry et al. (1995) *J. Biol. Chem.* 270(13):7304-10 ("Schultz-Cherry") or PCT International Application No. WO 91/08298 to Capon et al. ("Capon"). In the view of the examiner, at the time the invention was made, it would have been obvious for one of ordinary skill in the art to modify the method of Raychaudhuri comprising administering a composition comprising HPV E7 protein that is capable of inducing a CTL response against the HPV E7 protein, by co-administering a TGFβ-antagonizing agent in order to increase vaccine efficacy as described by Segarini, and/or to prevent TGFβ from stimulating growth of HPV-infected cells as described by Woodworth, as discussed above. Schultz-Cherry is further cited for its description of a thrombospondin peptide that binds to TGFβ and inhibits activation of latent TGFβ. The examiner relies on Capon as teaching a TGFβ receptor Fc-fusion protein. Advisory action, pages 7-8.

As discussed above with respect to the first rejection of claims under 35 U.S.C. §103(a), the combined teachings of Raychaudhuri, Woodworth, Segarini, and Schmolka do not establish a *prima facie* case of obviousness, because Raychaudhuri et al. does not describe or suggest the presently claimed method, and the cited secondary references would not have provided suggestion or motivation to one of ordinary skill in the art to modify the method of Raychaudhuri et al. to obtain the claimed invention with a reasonable expectation of success. In addition, the synergistic effects of the claimed combination are unexpected and further support the non-obviousness of the invention.

The failure of the cited references to establish a *prima facie* case of obviousness is not remedied by the additional teachings of Schultz-Cherry and/or Capon. These references described additional TGFβ inhibitors, but lack any teaching, suggestion, or motivation to combine such agents with an antigen formulation for administration to a patient having cervical

cancer. The applicants therefore respectfully request that the rejection of claim 47 under 35 U.S.C. §103(a), as allegedly unpatentable in view of Raychaudhuri, Woodworth, Segarini, Schmolka, Schultz-Cherry, and/or Capon be withdrawn.

Rejection of Claims Under The Doctrine of

Nonstatutory Obviousness Type Double Patenting

Claims 47, 51-65, and 68 are rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 1-2 and 4-19 of U.S. Patent No. 6,998,125. Advisory action, page 2. In response to this rejection, applicants submit that a terminal disclaimer will be considered when one or more claims of the instant application are in condition for allowance.

CONCLUSION

All rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a notice to that effect is earnestly solicited. If the examiner identifies any points that he feels may be best resolved through a personal or telephone interview, she is kindly requested to contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,

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By_____
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